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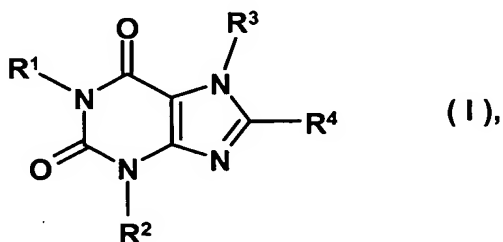
XANTHINE DERIVATIVES, THE PREPARATION THEREOF AND THEIR USE  
AS PHARMACEUTICAL COMPOSITIONS

10 **Related Applications**

The priority benefit of DE 102 54 304.6, filed November 21, 2002 and U.S. Provisional Application No. 60/432,450, filed December 11, 2002 are hereby claimed, both of which are incorporated by reference herein.

15 **Detailed Description**

The present invention relates to new substituted xanthines of general formula



20 the tautomers, enantiomers, diastereomers, the mixtures thereof, the prodrugs thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV), the preparation thereof, the use thereof  
25 for the prevention or treatment of diseases or conditions associated with an increased DPP-IV activity or capable of being prevented or alleviated by reducing the DPP-IV activity, particularly type I or type II diabetes mellitus, the pharmaceutical compositions containing a compound of general formula (I) or a physiologically acceptable salt thereof as well as processes for the preparation  
30 thereof.

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In the above formula I

R<sup>1</sup> represents an A-B-D group wherein

10 A denotes a C<sub>1-6</sub>-alkyl group substituted by a phenyl group, where the C<sub>1-6</sub>-alkyl group may be substituted by one to twelve fluorine atoms and the phenyl ring may be substituted by the groups R<sup>10</sup> to R<sup>14</sup> and

R<sup>10</sup> denotes a fluorine, chlorine, bromine or iodine atom,

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a C<sub>1-4</sub>-alkyl, hydroxy, or C<sub>1-4</sub>-alkyloxy group,

a nitro, amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)amino, cyano-C<sub>1-3</sub>-alkylamino, [N-(cyano-C<sub>1-3</sub>-alkyl)-N-C<sub>1-3</sub>-alkyl-amino], C<sub>1-3</sub>-alkyloxy-carbonyl-C<sub>1-3</sub>-alkylamino, 20 pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-(C<sub>1-3</sub>-alkyl)-piperazin-1-yl, C<sub>1-3</sub>-alkyl-carbonylamino, arylcarbonylamino, aryl-C<sub>1-3</sub>-alkyl-carbonylamino, C<sub>1-3</sub>-alkyloxy-carbonylamino, aminocarbonylamino, C<sub>1-3</sub>-alkyl-aminocarbonylamino, di-(C<sub>1-3</sub>-alkyl)aminocarbonylamino, C<sub>1-3</sub>-alkyl-sulphonylamino, bis-(C<sub>1-3</sub>-alkylsulphonyl)-amino, aminosulphonylamino, C<sub>1-3</sub>-alkylamino- 25 sulphonylamino, di-(C<sub>1-3</sub>-alkyl)amino-sulphonylamino, morpholin-4-yl-sulphonylamino, (C<sub>1-3</sub>-alkylamino)thiocarbonylamino, (C<sub>1-3</sub>-alkyloxy-carbonylamino)carbonylamino, arylsulphonylamino or aryl-C<sub>1-3</sub>-alkyl-sulphonylamino group,

30 an N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkyl-carbonylamino, N-(C<sub>1-3</sub>-alkyl)-arylcarbonylamino, N-(C<sub>1-3</sub>-alkyl)-aryl-C<sub>1-3</sub>-alkyl-carbonylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkyloxy-carbonylamino, N-(aminocarbonyl)-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl-aminocarbonyl)-C<sub>1-3</sub>-alkylamino, N-[di-(C<sub>1-3</sub>-alkyl)aminocarbonyl]-C<sub>1-3</sub>-alkylamino, N-(C<sub>1-3</sub>-alkyl)-C<sub>1-3</sub>-alkyl-sulphonylamino, N-(C<sub>1-3</sub>-alkyl)-arylsulphonylamino, or N-(C<sub>1-3</sub>-alkyl)- 35 aryl-C<sub>1-3</sub>-alkyl-sulphonylamino group,

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a 2-oxo-imidazolidin-1-yl, 2,4-dioxo-imidazolidin-1-yl or 2,5-dioxo-imidazolidin-1-yl group wherein the nitrogen atom in the 3 position may in each case be substituted by a methyl or ethyl group,

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a cyano, carboxy, C<sub>1-4</sub>-alkyloxy-carbonyl, aminocarbonyl, C<sub>1-3</sub>-alkyl-amino-carbonyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl or 4-(C<sub>1-3</sub>-alkyl)-piperazin-1-yl-carbonyl group,

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a C<sub>1-3</sub>-alkyl-carbonyl or an arylcarbonyl group,

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a carboxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkyloxy-carbonyl-C<sub>1-3</sub>-alkyl, cyano-C<sub>1-3</sub>-alkyl, aminocarbonyl-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkyl-aminocarbonyl-C<sub>1-3</sub>-alkyl, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl-C<sub>1-3</sub>-alkyl, pyrrolidin-1-yl-carbonyl-C<sub>1-3</sub>-alkyl, piperidin-1-yl-carbonyl-C<sub>1-3</sub>-alkyl, morpholin-4-yl-carbonyl-C<sub>1-3</sub>-alkyl, piperazin-1-yl-carbonyl-C<sub>1-3</sub>-alkyl or 4-(C<sub>1-3</sub>-alkyl)-piperazin-1-yl-carbonyl-C<sub>1-3</sub>-alkyl group,

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a carboxy-C<sub>1-3</sub>-alkyloxy, C<sub>1-3</sub>-alkyloxy-carbonyl-C<sub>1-3</sub>-alkyloxy, cyano-C<sub>1-3</sub>-alkyloxy, aminocarbonyl-C<sub>1-3</sub>-alkyloxy, C<sub>1-3</sub>-alkyl-aminocarbonyl-C<sub>1-3</sub>-alkyloxy, di-(C<sub>1-3</sub>-alkyl)-aminocarbonyl-C<sub>1-3</sub>-alkyloxy, pyrrolidin-1-yl-carbonyl-C<sub>1-3</sub>-alkyloxy, piperidin-1-yl-carbonyl-C<sub>1-3</sub>-alkyloxy, morpholin-4-yl-carbonyl-C<sub>1-3</sub>-alkyloxy, piperazin-1-yl-carbonyl-C<sub>1-3</sub>-alkyloxy or 4-(C<sub>1-3</sub>-alkyl)-piperazin-1-yl-carbonyl-C<sub>1-3</sub>-alkyloxy group,

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a hydroxy-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkyloxy-C<sub>1-3</sub>-alkyl, amino-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkylamino-C<sub>1-3</sub>-alkyl, di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl, pyrrolidin-1-yl-C<sub>1-3</sub>-alkyl, piperidin-1-yl-C<sub>1-3</sub>-alkyl, morpholin-4-yl-C<sub>1-3</sub>-alkyl, piperazin-1-yl-C<sub>1-3</sub>-alkyl, 4-(C<sub>1-3</sub>-alkyl)-piperazin-1-yl-C<sub>1-3</sub>-alkyl group,

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a hydroxy-C<sub>1-3</sub>-alkyloxy, C<sub>1-3</sub>-alkyloxy-C<sub>1-3</sub>-alkyloxy, C<sub>1-3</sub>-alkylsulphanyl-

5 C<sub>1-3</sub>-alkyloxy, C<sub>1-3</sub>-alkylsulphinyl-C<sub>1-3</sub>-alkyloxy, C<sub>1-3</sub>-alkylsulphonyl-C<sub>1-3</sub>-alkyloxy, amino-C<sub>1-3</sub>-alkyloxy, C<sub>1-3</sub>-alkylamino-C<sub>1-3</sub>-alkyloxy, di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyloxy, pyrrolidin-1-yl-C<sub>1-3</sub>-alkyloxy, piperidin-1-yl-C<sub>1-3</sub>-alkyloxy, morpholin-4-yl-C<sub>1-3</sub>-alkyloxy, piperazin-1-yl-C<sub>1-3</sub>-alkyloxy, 4-(C<sub>1-3</sub>-alkyl)-piperazin-1-yl-C<sub>1-3</sub>-alkyloxy group,

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a mercapto, C<sub>1-3</sub>-alkylsulphanyl, C<sub>1-3</sub>-alkylsulphinyl, arylsulphinyl, C<sub>1-3</sub>-alkylsulphonyl, arylsulphonyl, C<sub>1-3</sub>-alkylsulphonyloxy, arylsulphonyloxy, trifluoromethylsulphanyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

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a sulpho, aminosulphonyl, C<sub>1-3</sub>-alkyl-aminosulphonyl, di-(C<sub>1-3</sub>-alkyl)-aminosulphonyl, pyrrolidin-1-yl-sulphonyl, piperidin-1-yl-sulphonyl, morpholin-4-yl-sulphonyl, piperazin-1-yl-sulphonyl or 4-(C<sub>1-3</sub>-alkyl)-piperazin-1-yl-sulphonyl group,

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a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

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a C<sub>2-4</sub>-alkenyl or C<sub>2-4</sub>-alkynyl group,

a C<sub>3-4</sub>-alkenyloxy or C<sub>3-4</sub>-alkynyloxy group,

a C<sub>3-6</sub>-cycloalkyl or C<sub>3-6</sub>-cycloalkyloxy group,

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a C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl or C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyloxy group or

an aryl, aryloxy, aryl-C<sub>1-3</sub>-alkyl or aryl-C<sub>1-3</sub>-alkyloxy group,

5         $R^{11}$  and  $R^{12}$ , which may be identical or different, in each case denote a fluorine, chlorine, bromine or iodine atom, a  $C_{1-3}$ -alkyl, trifluoromethyl, hydroxy or  $C_{1-3}$ -alkyloxy group or a cyano group, or

10         $R^{11}$  together with  $R^{12}$ , if they are bound to adjacent carbon atoms, also denote a methylenedioxy, difluoromethylenedioxy, straight-chain  $C_{3-5}$ -alkylene or  $-CH=CH-CH=CH-$  group, while the  $-CH=CH-CH=CH-$  group may be substituted by a fluorine, chlorine or bromine atom, by a methyl, trifluoromethyl, cyano, aminocarbonyl, aminosulphonyl, methylsulphonyl, methylsulphonylamino, methoxy, difluoromethoxy or trifluoromethoxy group,  
15        and

20         $R^{13}$  and  $R^{14}$ , which may be identical or different, in each case represent a fluorine, chlorine or bromine atom, a trifluoromethyl,  $C_{1-3}$ -alkyl or  $C_{1-3}$ -alkyloxy group,

25        a phenyl group which may be substituted by the groups  $R^{10}$  to  $R^{14}$ , where  $R^{10}$  to  $R^{14}$  are as hereinbefore defined,

30        a phenyl- $C_{2-3}$ -alkenyl group wherein the phenyl moiety may be substituted by the groups  $R^{10}$  to  $R^{14}$ , where  $R^{10}$  to  $R^{14}$  are as hereinbefore defined, and the alkenyl group may be substituted by one to four fluorine atoms or methyl groups, while the substituents may be identical or different,

35        a phenyl- $C_{2-3}$ -alkynyl group wherein the phenyl moiety may be substituted by the groups  $R^{10}$  to  $R^{14}$ , where  $R^{10}$  to  $R^{14}$  are as hereinbefore defined,

40        a heteroaryl- $C_{1-6}$ -alkyl group, while the  $C_{1-6}$ -alkyl group may be substituted by one to twelve fluorine atoms,

45        a heteroaryl group,

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a heteroaryl-C<sub>2-3</sub>-alkenyl group, while the alkenyl group may be substituted by one to four fluorine atoms or methyl groups, while the substituents may be identical or different, or

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a heteroaryl-C<sub>2-3</sub>-alkynyl group and

B denotes an E-G group wherein E is linked to the group A and

E denotes an oxygen or sulphur atom,

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an -NR<sub>a</sub>- group wherein R<sub>a</sub> denotes a hydrogen atom, a C<sub>1-6</sub>-alkyl, C<sub>3-6</sub>-alkenyl, C<sub>3-6</sub>-alkynyl, C<sub>3-7</sub>-cycloalkyl, phenyl, phenylmethyl, heteroaryl, heteroarylmethyl, amino, C<sub>1-6</sub>-alkylamino, di-(C<sub>1-6</sub>-alkyl)amino, hydroxy, C<sub>1-6</sub>-alkyloxy group, while the above-mentioned phenyl rings may each be substituted by the groups R<sup>10</sup> to R<sup>11</sup>, while R<sup>10</sup> to R<sup>11</sup> are as hereinbefore defined,

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an -NR<sub>a</sub>-NR<sub>a</sub>- group wherein R<sub>a</sub> is as hereinbefore defined and the two groups R<sub>a</sub> may be identical or different,

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an -NH-NH- group wherein the two hydrogen atoms are replaced by a straight-chain C<sub>3-5</sub>-alkylene bridge,

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an -O-NR<sub>a</sub>- group wherein R<sub>a</sub> is as hereinbefore defined and the oxygen atom is linked to the group A and the nitrogen atom is linked to the group G,

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a -O-CR<sub>b</sub>R<sub>c</sub>- group wherein the oxygen atom is linked to the group A and the carbon atom is linked to the group G and wherein R<sub>b</sub> and R<sub>c</sub>, which may be identical or different, denote a hydrogen or fluorine atom, a C<sub>1-6</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, phenyl, phenylmethyl, while the phenyl rings may each be

5 substituted by the groups  $R^{10}$  to  $R^{14}$ , while  $R^{10}$  to  $R^{14}$  are as hereinbefore defined, or a heteroaryl or heteroarylmethyl group or  $R_b$  and  $R_c$  together denote a straight-chain  $C_{2-6}$ -alkylene group,

10 a  $-S-CR_bR_c-$  group wherein the sulphur atom is linked to the group A and the carbon atom is linked to the group G and  $R_b$  and  $R_c$ , which may be identical or different, are as hereinbefore defined,

15 a  $-SO-CR_bR_c-$  group wherein the sulphur atom is linked to the group A and the carbon atom is linked to the group G and  $R_b$  and  $R_c$ , which may be identical or different, are as hereinbefore defined,

a  $-SO_2-CR_bR_c-$  group wherein the sulphur atom is linked to the group A and the carbon atom is linked to the group G and  $R_b$  and  $R_c$ , which may be identical or different, are as hereinbefore defined,

20 or a  $-NR_a-CR_bR_c-$  group wherein the nitrogen atom is linked to the group A and the carbon atom is linked to the group G and  $R_a$ ,  $R_b$  and  $R_c$ , which may be identical or different, are as hereinbefore defined,

25 and G denotes a carbonyl or thiocarbonyl group,

a methylene group substituted by an imino group wherein the nitrogen atom may be substituted by a  $C_{1-6}$ -alkyl,  $C_{3-6}$ -alkenyl,  $C_{3-6}$ -alkynyl,  $C_{3-7}$ -cycloalkyl, phenyl, phenylmethyl, heteroaryl, heteroarylmethyl, amino,  $C_{1-6}$ -alkylamino, 30 di- $(C_{1-6}$ -alkyl)amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl,  $C_{1-6}$ -alkyl-carbonylamino, phenylcarbonylamino,  $C_{1-6}$ -alkyloxy-carbonylamino,  $C_{1-6}$ -alkylsulphonylamino, phenylsulphonylamino, hydroxyl,  $C_{1-6}$ -alkyloxy, cyano or nitro group, while the above-mentioned phenyl groups may be substituted by the groups  $R^{10}$  to  $R^{14}$ , where  $R^{10}$  to  $R^{14}$  are as hereinbefore 35 defined,

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a 1,1-ethenylene group wherein the carbon atom in the exo position may be substituted by one or two chlorine or fluorine atoms or one or two C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-perfluoroalkyl, C<sub>3-6</sub>-alkenyl, C<sub>3-6</sub>-alkynyl, C<sub>3-7</sub>-cycloalkyl, phenyl, phenylmethyl, heteroaryl, heteroarylmethyl, C<sub>1-6</sub>-alkyl-carbonyl, C<sub>3-7</sub>-cycloalkyl-carbonyl, phenylcarbonyl, heteroarylcarbonyl, carboxy, C<sub>1-6</sub>-alkyloxy-carbonyl, aminocarbonyl, C<sub>1-6</sub>-alkylaminocarbonyl, di-(C<sub>1-6</sub>-alkyl)aminocarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, phenylaminocarbonyl, heteroarylaminocarbonyl, C<sub>1-6</sub>-alkylsulphinyl, C<sub>3-7</sub>-cycloalkylsulphinyl, phenylsulphinyl, heteroarylsulphinyl, C<sub>1-6</sub>-alkylsulphonyl, C<sub>3-7</sub>-cycloalkylsulphonyl, phenylsulphonyl, heteroarylsulphonyl, cyano or nitro groups, while the substituents may be identical or different and the above-mentioned phenyl groups may be substituted by the groups R<sup>10</sup> to R<sup>14</sup>, while R<sup>10</sup> to R<sup>14</sup> are as hereinbefore defined,

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or represent a sulphinyl or sulphonyl group,

or A together with B denotes a 1,2,3,4-tetrahydroquinolinylcarbonyl, 1,2,3,4-tetrahydroisoquinolinylcarbonyl, 2,3-dihydroindolylcarbonyl or 2,3-dihydroisoindolylcarbonyl group wherein the benzo groups may in each case be substituted by the groups R<sup>10</sup> to R<sup>13</sup>, while R<sup>10</sup> to R<sup>13</sup> are as hereinbefore defined and one or two carbon atoms of the benzo group may be replaced by nitrogen atoms and the alkylene moieties of the above-mentioned groups may in each case be substituted by one or two fluorine atoms, one or two methyl groups or an oxo group, while the substituents may be identical or different,

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and D denotes a C<sub>1-6</sub>-alkylene group which may be substituted by one to twelve fluorine atoms,



5 a C<sub>2-3</sub>-alkenylene group which may be substituted by one to four fluorine atoms or methyl groups,

or a propynylene group,

10 R<sup>2</sup> denotes a hydrogen atom,

a C<sub>1-6</sub>-alkyl group,

a C<sub>2-4</sub>-alkenyl group,

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a C<sub>3-4</sub>-alkynyl group,

a C<sub>3-6</sub>-cycloalkyl group,

20 a C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl group,

a tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl or tetrahydropyranylmethyl group,

25 an aryl group,

an aryl-C<sub>1-4</sub>-alkyl group,

an aryl-C<sub>2-3</sub>-alkenyl group,

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an arylcarbonyl-C<sub>1-2</sub>-alkyl group,

a heteroaryl-C<sub>1-3</sub>-alkyl group,

5 a furanylcarbonylmethyl, thienylcarbonylmethyl, thiazolylcarbonylmethyl or pyridylcarbonylmethyl group,

a C<sub>1-4</sub>-alkyl-carbonyl-C<sub>1-2</sub>-alkyl group,

10 a C<sub>3-6</sub>-cycloalkyl-carbonyl-C<sub>1-2</sub>-alkyl group,

an aryl-G-C<sub>1-3</sub>-alkyl group, while G denotes an oxygen or sulphur atom, an imino, C<sub>1-3</sub>-alkylimino, sulphinyl or sulphonyl group,

15 a C<sub>1-4</sub>-alkyl group substituted by a group R<sub>d</sub>, wherein

R<sub>d</sub> denotes a cyano, carboxy, C<sub>1-3</sub>-alkyloxy-carbonyl, aminocarbonyl, C<sub>1-3</sub>-alkylamino-carbonyl, di-(C<sub>1-3</sub>-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

or a C<sub>2-4</sub>-alkyl group substituted by a group R<sub>e</sub>, where

R<sub>e</sub> denotes a hydroxy, C<sub>1-3</sub>-alkyloxy, amino, C<sub>1-3</sub>-alkylamino, di-(C<sub>1-3</sub>-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl or 4-ethyl-piperazin-1-yl group and is isolated from the cyclic nitrogen atom in the 3 position of the xanthine structure by at least two carbon atoms,

30 R<sup>3</sup> denotes a C<sub>3-8</sub>-alkyl group,

a C<sub>1-3</sub>-alkyl group substituted by a group R<sub>f</sub>, where

R<sub>f</sub> denotes a C<sub>3-7</sub>-cycloalkyl group optionally substituted by one or two C<sub>1-3</sub>-alkyl groups or

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a C<sub>5-7</sub>-cycloalkenyl group optionally substituted by one or two C<sub>1-3</sub>-alkyl groups,

a C<sub>3-8</sub>-alkenyl group,

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a C<sub>3-6</sub>-alkenyl group substituted by a fluorine, chlorine or bromine atom or a trifluoromethyl group,

a C<sub>3-8</sub>-alkynyl group,

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an aryl group or

an aryl-C<sub>2-4</sub>-alkenyl group,

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and

R<sup>4</sup> denotes an azetidin-1-yl or pyrrolidin-1-yl group which is substituted in the 3 position by an amino, C<sub>1-3</sub>-alkylamino or a di-(C<sub>1-3</sub>-alkyl)amino group and may additionally be substituted by one or two C<sub>1-3</sub>-alkyl groups,

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a piperidin-1-yl or hexahydroazepin-1-yl group which is substituted in the 3 position or in the 4 position by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)amino group and may additionally be substituted by one or two C<sub>1-3</sub>-alkyl groups,

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a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl-moiety is additionally substituted by an aminocarbonyl, C<sub>1-2</sub>-alkyl-aminocarbonyl, di-(C<sub>1-2</sub>-alkyl)aminocarbonyl, pyrrolidin-1-yl-carbonyl, (2-cyano-pyrrolidin-1-yl)carbonyl, thiazolidin-3-yl-carbonyl, (4-cyano-thiazolidin-3-yl)carbonyl, piperidin-1-ylcarbonyl or morpholin-4-ylcarbonyl group,

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5 a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl-moiety in the 4 position or in the 5 position is additionally substituted by a hydroxy or methoxy group,

a 3-amino-piperidin-1-yl group wherein the methylene group in the 2 position or in the 6 position is replaced by a carbonyl group,

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a piperidin-1-yl or hexahydroazepin-1-yl group substituted in the 3 position by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group, wherein in each case two hydrogen atoms on the carbon skeleton of the piperidin-1-yl or hexahydroazepin-1-yl- group are replaced by a straight-chain alkylene bridge, this bridge containing

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2 to 5 carbon atoms if the two hydrogen atoms are located on the same carbon atom, or 1 to 4 carbon atoms if the hydrogen atoms are located on adjacent carbon atoms, or 1 to 4 carbon atoms if the hydrogen atoms are located on carbon atoms separated by one atom, or 1 to 3 carbon atoms if the two hydrogen atoms are located on carbon atoms separated by two atoms,

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an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl or hexahydroazepin-1-yl group which is substituted by an amino-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkylamino-C<sub>1-3</sub>-alkyl or a di-(C<sub>1-3</sub>-alkyl)-amino-C<sub>1-3</sub>-alkyl group,

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a piperazin-1-yl or [1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two C<sub>1-3</sub>-alkyl groups, while in those compounds wherein

the group E denotes an oxygen atom and the group G denotes a carbonyl group,

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the group E denotes an oxygen atom and the group G denotes a sulphonyl group,

the group E denotes an -NR<sub>a</sub>- group and the group G denotes a carbonyl group wherein R<sub>a</sub> is as hereinbefore defined,

the group E denotes an -NR<sub>a</sub>- group wherein R<sub>a</sub> is as hereinbefore defined,

5           and the group G denotes a sulphonyl group or the group A denotes a phenyl or heteroaryl group optionally substituted by one of the above-mentioned groups and the group E denotes an oxygen atom and the group G denotes an ethenylene group,

10            $R^4$  cannot represent a piperazin-1-yl or [1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two  $C_{1-3}$ -alkyl groups,

          a 3-imino-piperazin-1-yl, 3-imino-[1,4]diazepan-1-yl or 5-imino-[1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two  $C_{1-3}$ -alkyl groups,

15           a [1,4]diazepan-1-yl group optionally substituted by one or two  $C_{1-3}$ -alkyl groups which is substituted in the 6 position by an amino group,

20           a  $C_{3-7}$ -cycloalkyl group which is substituted by an amino,  $C_{1-3}$ -alkylamino or di- $(C_{1-3}$ -alkyl)-amino group,

          a  $C_{3-7}$ -cycloalkyl group which is substituted by an amino- $C_{1-3}$ -alkyl,  $C_{1-3}$ -alkylamino- $C_{1-3}$ -alkyl or a di- $(C_{1-3}$ -alkyl)amino- $C_{1-3}$ -alkyl group,

25           a  $C_{3-7}$ -cycloalkyl- $C_{1-2}$ -alkyl group wherein the cycloalkyl moiety is substituted by an amino,  $C_{1-3}$ -alkylamino or di- $(C_{1-3}$ -alkyl)-amino group,

30           a  $C_{3-7}$ -cycloalkyl- $C_{1-2}$ -alkyl group wherein the cycloalkyl moiety is substituted by an amino- $C_{1-3}$ -alkyl,  $C_{1-3}$ -alkylamino- $C_{1-3}$ -alkyl or a di- $(C_{1-3}$ -alkyl)amino- $C_{1-3}$ -alkyl group,

          a  $C_{3-7}$ -cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino,  $C_{1-3}$ -alkylamino or di- $(C_{1-3}$ -alkyl)-amino group, while the two nitrogen atoms

5 on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

an N-(C<sub>3-7</sub>-cycloalkyl)-N-(C<sub>1-3</sub>-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group, while the  
10 two nitrogen atoms on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

a C<sub>3-7</sub>-cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkylamino-C<sub>1-3</sub>-alkyl or a di-(C<sub>1-3</sub>-alkyl)amino-C<sub>1-3</sub>-alkyl  
15 group,

an N-(C<sub>3-7</sub>-cycloalkyl)-N-(C<sub>1-3</sub>-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkylamino-C<sub>1-3</sub>-alkyl or a di-(C<sub>1-3</sub>-alkyl)amino-C<sub>1-3</sub>-alkyl group,  
20

a C<sub>3-7</sub>-cycloalkyl-C<sub>1-2</sub>-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

an N-(C<sub>3-7</sub>-cycloalkyl-C<sub>1-2</sub>-alkyl)-N-(C<sub>1-2</sub>-alkyl)-amino group wherein the cycloalkyl  
25 moiety is substituted by an amino, C<sub>1-3</sub>-alkylamino or di-(C<sub>1-3</sub>-alkyl)-amino group,

a C<sub>3-7</sub>-cycloalkyl-C<sub>1-2</sub>-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkylamino-C<sub>1-3</sub>-alkyl or a di-(C<sub>1-3</sub>-alkyl)amino-C<sub>1-3</sub>-alkyl group,  
30

an N-(C<sub>3-7</sub>-cycloalkyl-C<sub>1-2</sub>-alkyl)-N-(C<sub>1-2</sub>-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkylamino-C<sub>1-3</sub>-alkyl or a di-(C<sub>1-3</sub>-alkyl)amino-C<sub>1-3</sub>-alkyl group,

- 5 a  $R^{19}$ - $C_{2-4}$ -alkylamino group wherein  $R^{19}$  is separated from the nitrogen atom of the  $C_{2-4}$ -alkylamino moiety by at least two carbon atoms and

$R^{19}$  denotes an amino,  $C_{1-3}$ -alkylamino or di- $(C_{1-3}$ -alkyl)-amino group,

- 10 an  $R^{19}$ - $C_{2-4}$ -alkylamino group wherein the nitrogen atom of the  $C_{2-4}$ -alkylamino moiety is substituted by a  $C_{1-3}$ -alkyl group and  $R^{19}$  is separated from the nitrogen atom of the  $C_{2-4}$ -alkylamino moiety by at least two carbon atoms, while  $R^{19}$  is as hereinbefore defined,

- 15 an amino group substituted by the group  $R^{20}$  wherein

- $R^{20}$  denotes an azetidin-3-yl, azetidin-2-ylmethyl, azetidin-3-ylmethyl, pyrrolidin-3-yl, pyrrolidin-2-ylmethyl, pyrrolidin-3-ylmethyl, piperidin-3-yl, piperidin-4-yl, piperidin-2-ylmethyl, piperidin-3-ylmethyl or piperidin-4-ylmethyl group, while the groups mentioned for  $R^{20}$  may in each case be substituted by one or two  $C_{1-3}$ -alkyl groups,
- 20

- an amino group substituted by the group  $R^{20}$  and a  $C_{1-3}$ -alkyl group wherein  $R^{20}$  is as hereinbefore defined, while the groups mentioned for  $R^{20}$  may in each case be substituted by one or two  $C_{1-3}$ -alkyl groups,
- 25

- an  $R^{19}$ - $C_{3-4}$ -alkyl group wherein the  $C_{3-4}$ -alkyl moiety is straight-chain and may additionally be substituted by one or two  $C_{1-3}$ -alkyl groups, while  $R^{19}$  is as hereinbefore defined,
- 30

- a 3-amino-2-oxo-piperidin-5-yl or 3-amino-2-oxo-1-methyl-piperidin-5-yl group,

- a pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, hexahydroazepin-3-yl or hexahydroazepin-4-yl group which is substituted in the 1 position by an amino,  $C_{1-3}$ -alkylamino or di- $(C_{1-3}$ -alkyl)amino group,
- 35

5

or an azetidin-2-yl-C<sub>1-2</sub>-alkyl, azetidin-3-yl-C<sub>1-2</sub>-alkyl, pyrrolidin-2-yl-C<sub>1-2</sub>-alkyl, pyrrolidin-3-yl, pyrrolidin-3-yl-C<sub>1-2</sub>-alkyl, piperidin-2-yl-C<sub>1-2</sub>-alkyl, piperidin-3-yl, piperidin-3-yl-C<sub>1-2</sub>-alkyl, piperidin-4-yl or piperidin-4-yl-C<sub>1-2</sub>-alkyl group, while the above-mentioned groups may in each case be substituted by one or two C<sub>1-3</sub>-alkyl groups,

10

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, which may be mono- or disubstituted by R<sub>n</sub> independently of one another, where the substituents are identical or different and R<sub>n</sub> denotes a fluorine, chlorine, bromine or iodine atom, a trifluoromethyl, cyano, nitro, amino, aminocarbonyl, aminosulphonyl, methylsulphonyl, acetylamino, methylsulphonylamino, C<sub>1-4</sub>-alkyl, C<sub>1-3</sub>-alkyl-carbonyl, cyclopropyl, ethenyl, ethynyl, hydroxy, C<sub>1-4</sub>-alkyloxy, C<sub>1-4</sub>-alkoxy-carbonyl, methylsulphanyl, phenylsulphanyl, methylsulphonyl, phenylsulphonyl, difluoromethoxy or trifluoromethoxy group,

20

by the heteroaryl groups mentioned in the definitions of the above-mentioned groups are meant a pyrrolyl, furanyl, thienyl, pyridyl, indolyl, benzofuranyl, benzothiophenyl, quinolinyl or isoquinolinyl group,

25

or a pyrrolyl, furanyl, thienyl or pyridyl group wherein one or two methyne groups are replaced by nitrogen atoms,

or an indolyl, benzofuranyl, benzothiophenyl, quinolinyl or isoquinolinyl group wherein one to three methyne groups are replaced by nitrogen atoms,

30

or a 1,2-dihydro-2-oxo-pyridinyl, 1,4-dihydro-4-oxo-pyridinyl, 2,3-dihydro-3-oxo-pyridazinyl, 1,2,3,6-tetrahydro-3,6-dioxo-pyridazinyl, 1,2-dihydro-2-oxo-pyrimidinyl, 3,4-dihydro-4-oxo-pyrimidinyl, 1,2,3,4-tetrahydro-2,4-dioxo-pyrimidinyl, 1,2-dihydro-2-oxo-pyrazinyl, 1,2,3,4-tetrahydro-2,3-dioxo-pyrazinyl, 2,3-dihydro-2-oxo-indolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-oxo-1*H*-benzimidazolyl, 2,3-

35



5 dihydro-2-oxo-benzoxazolyl, 1,2-dihydro-2-oxo-quinoliny, 1,4-dihydro-4-oxo-quinoliny, 1,2-dihydro-1-oxo-isoquinoliny, 1,4-dihydro-4-oxo-cinnoliny, 1,2-dihydro-2-oxo-quinazoliny, 3,4-dihydro-4-oxo-quinazoliny, 1,2,3,4-tetrahydro-2,4-dioxo-quinazoliny, 1,2-dihydro-2-oxoquinoxaliny, 1,2,3,4-tetrahydro-2,3-dioxo-quinoxaliny, 1,2-dihydro-1-oxo-phthalaziny, 1,2,3,4-tetrahydro-1,4-dioxo-phthalaziny, chromanyl, cumariny, 2,3-dihydro-benzo[1,4]dioxiny or 3,4-dihydro-10 3-oxo-2*H*-benzo[1,4]oxaziny group,

and the above-mentioned heteroaryl groups may be mono- or disubstituted by R<sub>h</sub>, while the substituents may be identical or different and R<sub>h</sub> is as  
15 hereinbefore defined,

and, unless otherwise stated, the above-mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

20 the tautomers, the enantiomers, the diastereomers, the mixtures thereof, the prodrugs thereof and the salts thereof.

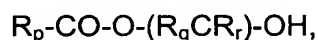
Compounds which contain a group that can be cleaved *in vivo* are prodrugs of the corresponding compounds wherein this group which can be cleaved *in vivo* has  
25 been cleaved.

The carboxy groups mentioned in the definition of the above-mentioned groups may be replaced by a group which can be converted into a carboxy group *in vivo* or by a group which is negatively charged under physiological conditions,  
30

and furthermore the amino and imino groups mentioned in the definition of the above-mentioned groups may be substituted by a group which can be cleaved *in vivo*. Such groups are described for example in WO 98/46576 and by N.M. Nielsen *et al.* in International Journal of Pharmaceutics 39, 75-85 (1987).  
35

5 By a group which can be converted *in vivo* into a carboxy group is meant, for  
 example, a hydroxymethyl group, a carboxy group esterified with an alcohol  
 wherein the alcohol moiety is preferably a C<sub>1-6</sub>-alkanol, a phenyl-C<sub>1-3</sub>-alkanol, a  
 C<sub>3-9</sub>-cycloalkanol, while a C<sub>5-8</sub>-cycloalkanol may additionally be substituted by one  
 or two C<sub>1-3</sub>-alkyl groups, a C<sub>5-8</sub>-cycloalkanol wherein a methylene group in the 3 or  
 10 4 position is replaced by an oxygen atom or by an imino group optionally  
 substituted by a C<sub>1-3</sub>-alkyl, phenyl-C<sub>1-3</sub>-alkyl, phenyl-C<sub>1-3</sub>-alkyloxycarbonyl or  
 C<sub>2-6</sub>-alkanoyl group and the cycloalkanol moiety may additionally be substituted by  
 one or two C<sub>1-3</sub>-alkyl groups, a C<sub>4-7</sub>-cycloalkenol, a C<sub>3-5</sub>-alkenol, a phenyl-  
 C<sub>3-5</sub>-alkenol, a C<sub>3-5</sub>-alkynol or phenyl-C<sub>3-5</sub>-alkynol with the proviso that no bonds to  
 15 the oxygen atom start from a carbon atom which carries a double or triple bond, a  
 C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms  
 which may additionally be substituted in the bicycloalkyl moiety by one or two  
 C<sub>1-3</sub>-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula

20



wherein

25  $R_p$  denotes a C<sub>1-8</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl, C<sub>1-8</sub>-alkyloxy, C<sub>5-7</sub>-cycloalkyloxy,  
 phenyl or phenyl-C<sub>1-3</sub>-alkyl group,

$R_q$  denotes a hydrogen atom, a C<sub>1-3</sub>-alkyl, C<sub>5-7</sub>-cycloalkyl or phenyl group  
 and

30

$R_r$  denotes a hydrogen atom or a C<sub>1-3</sub>-alkyl group,

by a group which is negatively charged under physiological conditions is meant,  
 for example, a tetrazol-5-yl, phenylcarbonylaminocarbonyl,  
 35 trifluoromethylcarbonylaminocarbonyl, C<sub>1-6</sub>-alkylsulphonylamino,

- 5 phenylsulphonylamino, benzylsulphonylamino, trifluoromethylsulphonylamino, C<sub>1-6</sub>-alkylsulphonylamino, phenylsulphonylamino, benzylsulphonylamino or perfluoro-C<sub>1-6</sub>-alkylsulphonylamino group
- 10 and by a group which can be cleaved *in vivo* from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as a phenylcarbonyl group optionally mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkyloxy groups, while the substituents may be identical or different, a pyridinoyl group or a C<sub>1-16</sub>-alkanoyl group such as the
- 15 formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, a 3,3,3-trichloropropionyl or allyloxycarbonyl group, a C<sub>1-16</sub>-alkyloxycarbonyl or C<sub>1-16</sub>-alkylcarbonyloxy group, wherein hydrogen atoms may be wholly or partially replaced by fluorine or chlorine atoms such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl,
- 20 tert.butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, hexadecyloxycarbonyl, methylcarbonyloxy, ethylcarbonyloxy, 2,2,2-trichloroethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy, butylcarbonyloxy, tert.butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, octylcarbonyloxy,
- 25 nonylcarbonyloxy, decylcarbonyloxy, undecylcarbonyloxy, dodecylcarbonyloxy or hexadecylcarbonyloxy group, a phenyl-C<sub>1-6</sub>-alkyloxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a 3-amino-propionyl group wherein the amino group may be mono- or disubstituted by C<sub>1-6</sub>-alkyl or C<sub>3-7</sub>-cycloalkyl groups and the substituents may be identical or
- 30 different, a C<sub>1-3</sub>-alkylsulphonyl-C<sub>2-4</sub>-alkyloxycarbonyl, C<sub>1-3</sub>-alkyloxy-C<sub>2-4</sub>-alkyloxy-C<sub>2-4</sub>-alkyloxycarbonyl, R<sub>p</sub>-CO-O-(R<sub>q</sub>CR<sub>r</sub>)-O-CO, C<sub>1-6</sub>-alkyl-CO-NH-(R<sub>s</sub>CR<sub>t</sub>)-O-CO or C<sub>1-6</sub>-alkyl-CO-O-(R<sub>s</sub>CR<sub>t</sub>)-(R<sub>s</sub>CR<sub>t</sub>)-O-CO group, wherein R<sub>p</sub> to R<sub>r</sub> are as hereinbefore defined,

- 5             $R_s$  and  $R_t$ , which may be identical or different, denote hydrogen atoms or  $C_{1-3}$ -alkyl groups.

Moreover, the saturated alkyl and alkyloxy moieties which contain more than 2 carbon atoms mentioned in the foregoing definitions and those that follow, unless  
10 otherwise stated, also include the branched isomers thereof such as, for example, the isopropyl, tert.butyl, isobutyl group, etc.

Preferred compounds of general formula I are those wherein

- 15     $R^1$ ,  $R^2$  and  $R^3$  are as hereinbefore defined and

$R^4$  denotes a pyrrolidin-1-yl group which is substituted in the 3 position by an amino group,

- 20    a piperidin-1-yl group which is substituted in the 3 position by an amino group,

a hexahydroazepin-1-yl- group which is substituted in the 3 position or in the 4 position by an amino group,

- 25    a (2-aminocyclohexyl)amino group,

a cyclohexyl group which is substituted in the 3 position by an amino group, or

an *N*-(2-aminoethyl)-*N*-methylamino or an *N*-(2-aminoethyl)-*N*-ethylamino group,

30

while, unless otherwise mentioned, the above-mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

the tautomers, the enantiomers, the diastereomers, the mixtures thereof and the  
35 salts thereof.

5

Particularly preferred are those compounds of general formula I wherein

$R^1$  denotes an A-B-D group wherein

10 A denotes a phenyl, phenylmethyl, 1-phenylethyl, pyridinyl, pyridinylmethyl, 1-pyridinylethyl, pyrimidinyl, pyrimidinylmethyl, pyrazinyl, pyrazinylmethyl, 1,3,5-triazinyl, 1,3,5-triazinylmethyl, 1,2,4-triazinyl, 1,2,4-triazinylmethyl, furanyl, thienyl, pyrrolyl, imidazolyl, 1,3-oxazolyl group, while the above-mentioned phenyl and heteroaryl groups may be substituted by a fluorine, 15 chlorine or bromine atom or by a  $C_{1-4}$ -alkyl,  $C_{1-4}$ -alkoxy, trifluoromethyl, cyano,  $C_{1-3}$ -alkyl-carbonyl,  $C_{1-4}$ -alkoxy-carbonyl, methylsulphinyl, phenylsulphinyl, methylsulphonyl, phenylsulphonyl, amino or nitro group and may optionally additionally be substituted by a fluorine, chlorine or bromine atom or by a  $C_{1-4}$ -alkyl,  $C_{1-4}$ -alkoxy, trifluoromethyl or cyano group, 20 while the substituents may be identical or different, and

B denotes an E-G group wherein E is linked to the group A and

25 E denotes an oxygen atom, an  $-NH-$ ,  $-N(CH_3)-$  or  $-NH-NH-$  group or a  $-OCH_2-$  group wherein the oxygen atom is linked to the group A and the carbon atom is linked to the group G, and

G denotes a carbonyl group,

30 a cyanoiminomethylene or nitroiminomethylene group

or a 1,1-ethenylene group wherein the carbon atom in the exo position may be substituted by one or two trifluoromethyl, cyano, nitro,

35  $C_{1-3}$ -alkyloxy-carbonyl,  $C_{1-4}$ -alkyl-carbonyl, phenylcarbonyl,  $C_{1-3}$ -alkylsulphinyl, phenylsulphinyl,  $C_{1-3}$ -alkylsulphonyl or

5           phenylsulphonyl groups, while the substituents may be identical or  
different and the above-mentioned phenyl groups may be substituted by  
one or two fluorine, chlorine or bromine atoms or one or two C<sub>1-3</sub>-alkyl,  
trifluoromethyl, C<sub>1-3</sub>-alkoxy, cyano, C<sub>1-3</sub>-alkyl-carbonyl, C<sub>1-3</sub>-alkoxy-  
carbonyl, methylsulphinyl, phenylsulphinyl, methylsulphonyl,  
10           phenylsulphonyl or nitro groups, while these substituents may also be  
identical or different,

          or A and B together denote a 1,2,3,4-tetrahydroquinolin-1-ylcarbonyl or  
1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl group and

15           D denotes a methylene group,

          R<sup>2</sup> denotes a hydrogen atom,

20           or a C<sub>1-3</sub>-alkyl group,

          R<sup>3</sup> denotes a C<sub>4-6</sub>-alkenyl group,

          a 2-butyne-1-yl group or

25           a 1-cyclopenten-1-yl-methyl group

          and

30           R<sup>4</sup> denotes a piperidin-1-yl group which is substituted in the 3 position by an amino  
group,

          a hexahydroazepin-1-yl- group which is substituted in the 3 position or in the 4  
position by an amino group,

35

5 a (2-aminocyclohexyl)amino group,

a cyclohexyl group which is substituted in the 3 position by an amino group, or

an *N*-(2-aminoethyl)-*N*-methylamino or an *N*-(2-aminoethyl)-*N*-ethylamino group,

10

while, unless otherwise mentioned, the above-mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

the tautomers, the enantiomers, the diastereomers, the mixtures thereof and the salts thereof.

15

Most particularly preferred are those compounds of general formula I, wherein

$R^1$  denotes an A-B-D group wherein

20

A denotes a phenyl, phenylmethyl, 1-phenylethyl, pyridinyl, pyridinylmethyl, 1-pyridinylethyl, pyrimidinyl or pyrimidinylmethyl group, where the phenyl moiety may be substituted by a fluorine, chlorine or bromine atom or by a  $C_{1-4}$ -alkyl, trifluoromethyl,  $C_{1-4}$ -alkoxy, cyano,  $C_{1-3}$ -alkyl-carbonyl,  $C_{1-4}$ -alkoxy-carbonyl, methylsulphinyl, phenylsulphinyl, methylsulphonyl, phenylsulphonyl, amino or nitro group and may optionally additionally be substituted by a fluorine, chlorine or bromine atom or by a  $C_{1-4}$ -alkyl, trifluoromethyl,  $C_{1-4}$ -alkoxy or cyano group, while the substituents may be identical or different, and

25

30

B denotes a E-G group wherein E is linked to the group A and

E denotes an oxygen atom, an -NH- group, -N(CH<sub>3</sub>)- group or -OCH<sub>2</sub>- group wherein the oxygen atom is linked to the group A and the carbon atom is linked to the group G, and

35

5

G denotes a carbonyl group,

or A and B together denote a 1,2,3,4-tetrahydroquinolin-1-ylcarbonyl or  
1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl group and

10

D denotes a methylene group,

$R^2$  denotes a methyl group,

15

$R^3$  denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group or

a 2-butyn-1-yl group

and

20

$R^4$  denotes a (3-amino-piperidin-1-yl) group,

the tautomers, the enantiomers, the diastereomers, the mixtures thereof and the  
salts thereof,

25

but particularly those compounds of general formula I wherein

$R^1$  denotes an A-B-D group wherein

30

A denotes a phenyl, phenylmethyl, pyridinyl or pyridinylmethyl group wherein  
the phenyl rings may be substituted by an amino, methoxy, methyl, cyano or  
nitro group, and

B denotes an E-G group wherein E is linked to the group A and

35



5 E denotes an oxygen atom, an -NH- group or -OCH<sub>2</sub>- group wherein the oxygen atom is linked to the group A and the carbon atom is linked to the group G, and

G denotes a carbonyl group,  
10 or A and B together denote a 1,2,3,4-tetrahydroquinolin-1-ylcarbonyl or 1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl group and

D denotes a methylene group,

15 R<sup>2</sup> denotes a methyl group,

R<sup>3</sup> denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group or

20 a 2-butyne-1-yl group

and

R<sup>4</sup> denotes a (3-amino-piperidin-1-yl) group,

25 the tautomers, the enantiomers, the diastereomers, the mixtures thereof and the salts thereof.

30 The following compounds of general formula I are particularly preferred:

(a) 1-[(benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine,

5 (b) 1-[(benzylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine,

(c) 1-[(phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine,

10

(d) 1-[[pyridin-2-yl]aminocarbonyl]methyl-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine,

(e) 1-[[pyridin-3-yl]methoxycarbonyl]methyl-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine,

15

(f) 1-[[pyridin-3-yl]aminocarbonyl]methyl-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine,

20 (g) 1-[[2-methyl-phenyl]aminocarbonyl]methyl-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine,

(h) 1-[[2-nitro-phenyl]aminocarbonyl]methyl-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine,

25

(i) 1-[[4-cyano-phenyl]aminocarbonyl]methyl-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

(j) 1-[[2-methoxy-phenyl]aminocarbonyl]methyl-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine,

30

(k) 1-(2-oxo-3-phenoxy-propyl)-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

5 (l) 1-[(2-amino-benzylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

(m) 1-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-  
[(*R*)-3-amino-piperidin-1-yl]-xanthine,

10

(n) 1-[2-(3,4-dihydro-2*H*-quinolin-1-yl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-  
[(*R*)-3-amino-piperidin-1-yl]-xanthine,

(o) 1-[[3-(3-cyano-phenyl)aminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-  
15 amino-piperidin-1-yl)-xanthine,

(p) 1-[(3-methoxy-benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-  
amino-piperidin-1-yl]-xanthine and

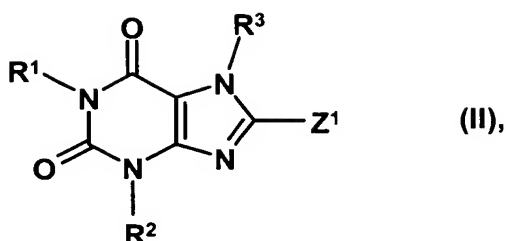
20 (q) 1-[(3-nitro-benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

and the salts thereof.

25 According to the invention the compounds of general formula I are obtained by methods known *per se*, for example by the following methods:

a) In order to prepare compounds of general formula I wherein R<sup>4</sup> is one of the groups mentioned hereinbefore, linked to the xanthine structure via a nitrogen  
30 atom:

reacting a compound of general formula



5

wherein

$R^1$  to  $R^3$  are as hereinbefore defined and

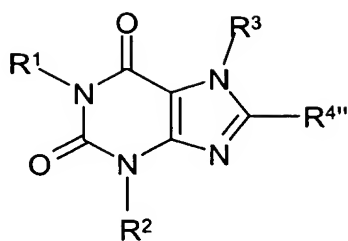
$Z^1$  denotes a leaving group such as a halogen atom, a substituted hydroxy,  
 10 mercapto, sulphinyl, sulphonyl or sulphonyloxy group, such as for example a  
 chlorine or bromine atom, a methanesulphonyl or methanesulphonyloxy group,  
 with an amine of general formula  $R^{4'}-H$ , wherein  $R^{4'}$  denotes one of the groups  
 mentioned for  $R^4$  hereinbefore which is linked to the xanthine structure via a  
 nitrogen atom.

15

The reaction is expediently carried out in a solvent such as isopropanol, butanol,  
 tetrahydrofuran, dioxane, dimethylformamide, dimethylsulphoxide, ethyleneglycol -  
 monomethylether, ethyleneglycol diethylether or sulpholane, optionally in the  
 presence of an inorganic or tertiary organic base, e.g. sodium carbonate,  
 20 potassium carbonate or potassium hydroxide, a tertiary organic base, e.g.  
 triethylamine, or in the presence of N-ethyl-diisopropylamine (Hünig base), while  
 these organic bases may simultaneously also serve as solvent, and optionally in  
 the presence of a reaction accelerator such as an alkali metal halide or a  
 palladium-based catalyst at temperatures between  $-20$  and  $180^\circ\text{C}$ , but preferably  
 25 at temperatures between  $-10$  and  $120^\circ\text{C}$ . The reaction may, however, also be  
 carried out without a solvent or in an excess of the amine of general formula  $R^{4'}-H$ .

30

b) Deprotecting a compound of general formula



(III),

wherein  $R^1$ ,  $R^2$  and  $R^3$  are as hereinbefore defined and

$R^{4''}$  denotes one of the groups mentioned for  $R^4$  hereinbefore which contain

an imino, amino or alkylamino group, while the imino, amino or alkylamino group

is substituted by a protective group, optionally followed by subsequent alkylation of the imino, amino or  $C_{1-3}$ -alkylamino group.

The liberating of an amino group from a protected precursor is a standard reaction in synthetic organic chemistry. There are many examples of suitable protective

groups. A summary of the chemistry of protective groups can be found in

Theodora W. Greene and Peter G. M. Wuts, *Protective Groups in Organic*

*Synthesis*, Second Edition, 1991, published by John Wiley and Sons, and in Philip J. Kocienski, *Protecting Groups*, published by Georg Thieme, 1994.

The following are examples of protective groups:

the tert.-butoxycarbonyl group which can be cleaved by treating with an acid

such as for example trifluoroacetic acid or hydrochloric acid or by treating with

bromotrimethylsilane or iodotrimethylsilane, optionally using a solvent such as

methylene chloride, ethyl acetate, dioxane, methanol, isopropanol or diethylether at temperatures between  $0^\circ\text{C}$  and  $80^\circ\text{C}$ ,

the 2,2,2-trichloroethoxycarbonyl group which can be cleaved by treating with

metals such as for example zinc or cadmium in a solvent such as acetic acid or a

- 5 mixture of tetrahydrofuran and a weak aqueous acid at temperatures between 0°C and the boiling temperature of the solvent used and

the carbobenzyloxycarbonyl group which can be cleaved for example by hydrogenolysis in the presence of a noble metal catalyst such as for example  
10 palladium-charcoal and a solvent such as for example alcohols, ethyl acetate, dioxane, tetrahydrofuran or mixtures of these solvents at temperatures between 0°C and the boiling point of the solvent, by treating with boron tribromide in methylene chloride at temperatures between -20°C and ambient temperature, or by treating with aluminium chloride/anisol at temperatures between 0°C and  
15 ambient temperature.

A C<sub>1-3</sub>-alkyl group may optionally be introduced subsequently by alkylation or reductive alkylation.

- 20 The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethyl sulphate, optionally in the presence of a  
25 tertiary organic base or in the presence of an inorganic base, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

- The subsequent reductive alkylation is carried out with a corresponding carbonyl  
30 compound such as formaldehyde, acetaldehyde, propionaldehyde or acetone in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride conveniently at a pH of 6-7 and at ambient temperature or in the presence of a hydrogenation catalyst, e.g. with hydrogen in the presence of palladium/charcoal,  
35 at a hydrogen pressure of 1 to 5 bar. The methylation may also be carried out in

- 5 the presence of formic acid as reducing agent at elevated temperatures, e.g. at temperatures between 60 and 120°C.

In the reactions described hereinbefore, any reactive groups present such as carboxy, amino, alkylamino or imino groups may be protected during the reaction  
10 by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group,

- 15 protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

- 20 Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically,  
25 e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

- However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such  
30 as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved  
35 in trifluoroacetic acid in the presence of anisole.

5

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane optionally using a solvent such as methylene chloride, dioxane, methanol or diethylether.

10

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution optionally in the presence of a solvent such as tetrahydrofuran at temperatures  
15 between 0 and 50°C.

20

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between  
20 and 50°C.

25

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and  
25 compounds with at least one optically active carbon atom may be separated into their enantiomers.

30

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained  
30 which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by  
35 chromatography and/or fractional crystallisation, and, if these compounds are



- 5 obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an  
10 optically active substance which forms racemic salts or derivatives such as e.g. esters or amides of an optically active substance, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric  
15 salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-O-p-toluoyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+)- or (-)-menthol and an optically active acyl group in amides, for  
20 example, may be a (+)- or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for  
25 example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy  
30 group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

35

- 5 The compounds of general formulae II and III used as starting materials are either known from the literature or may be obtained by methods known from the literature (cf. Examples I to VIII).

As already mentioned hereinbefore, the compounds of general formula I according  
10 to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on the enzyme DPP-IV.

The biological properties of the new compounds were investigated as follows:

- 15 The ability of the substances and their corresponding salts to inhibit the DPP-IV activity can be demonstrated in a test set-up in which an extract of human colon carcinoma cell line Caco-2 is used as the DPP IV source. The differentiation of the cells in order to induce the DPP-IV expression was carried out as described by Reiher et al. in an article entitled "Increased expression of intestinal cell line Caco-  
20 2" , which appeared in Proc. Natl. Acad. Sci. Vol. 90, pages 5757-5761 (1993). The cell extract was obtained from cells solubilised in a buffer (10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5% Nonidet-P40, pH 8.0) by centrifuging at 35,000 g for 30 minutes at 4°C (to remove cell debris).

- 25 The DPP-IV assay was carried out as follows:

50 µl substrate solution (AFC; AFC is amido-4-trifluoromethylcoumarin), final concentration 100 µM, were placed in black microtitre plates. 20 µl of assay buffer (final concentrations 50 mM Tris HCl pH 7.8, 50 mM NaCl, 1 % DMSO) was  
30 pipetted in. The reaction was started by adding 30 µl of solubilised Caco-2 protein (final concentration 0.14 µg of protein per well). The test substances to be investigated were typically added prediluted in 20 µl, and the volume of assay buffer was then reduced accordingly. The reaction was carried out at ambient temperature, incubating for 60 minutes. Then the fluorescence was measured in a  
35 Victor 1420 Multilabel Counter, the excitation wavelength being 405 nm and the

- 5 emission wavelength being 535 nm. Blank readings (corresponding to 0 % activity) were obtained in mixtures without any Caco-2 protein (volume replaced by assay buffer), control values (corresponding to 100 % activity) were obtained in mixtures with no substance added. The potency of the test substances in question, expressed as  $IC_{50}$  values, was calculated from dosage/activity curves consisting of
- 10 11 measuring points in each case. The following results were obtained:

Compound (Example No.)	DPP IV inhibition $IC_{50}$ [nM]
1	27
1(1)	46
1(2)	26
1(3)	4
1(4)	13
1(5)	7
1(6)	722
1(7)	4
1(8)	42
1(9)	32
1(10)	286
1(11)	28

- The compounds prepared according to the invention are well tolerated, as for example when 10 mg/kg of the compound of Example 1(3) were administered to
- 15 rats by oral route no changes in the animals' behaviour could be detected.

- In view of their ability to inhibit DPP-IV activity, the compounds of general formula I according to the invention and the corresponding pharmaceutically acceptable salts thereof are suitable for treating all those conditions or illnesses which can be
- 20 influenced by the inhibition of the DPP-IV activity. It is therefore to be expected that the compounds according to the invention will be suitable for the prevention or

5 treatment of diseases or conditions such as type I and type II diabetes mellitus, diabetic complications, metabolic acidosis or ketosis, insulin resistance, dyslipidaemias of various origins, arthritis, atherosclerosis and related diseases, obesity, allograft transplantation and calcitonin-induced osteoporosis. In addition these substances are capable of preventing B-cell degeneration such as e.g.

10 apoptosis or necrosis of pancreatic B-cells. The substances are also suitable for improving or restoring the function of pancreatic cells and also increasing the number and size of pancreatic B-cells. Additionally, and on the basis of the role of the Glucagon-Like Peptides, such as e.g. GLP-1 and GLP-2 and their link with DPP-IV inhibition, it is likely that the compounds according to the invention are

15 suitable for achieving, *inter alia*, a sedative or anxiety-relieving effect and also of favourably affecting catabolic states after operations or hormonal stress responses or of reducing mortality and morbidity after myocardial infarct. They are also suitable for treating all conditions which are connected with the above-mentioned effects and which are mediated by GLP-1 or GLP-2. The compounds according to

20 the invention may also be used as diuretics or antihypertensives and are suitable for preventing and treating acute renal failure. They are also suitable for the prevention and treatment of chronic inflammatory intestinal diseases. It is also expected that DPP-IV inhibitors and hence also the compounds according to the invention may be used to treat infertility or to improve fertility in humans or

25 mammals, particularly when the infertility is connected with insulin resistance or polycystic ovary syndrome. The substances are also suitable for treating deficiencies of growth hormone which are associated with reduced stature.

The compounds according to the invention may also be used in conjunction with

30 other active substances. Therapeutic agents which are suitable for such combinations include, for example, antidiabetics, such as metformin, sulphonylureas (e.g. glibenclamid, tolbutamide, glimepiride), nateglinide, repaglinide, thiazolidinedione (e.g. rosiglitazone, pioglitazone), PPAR-gamma agonists (e.g. GI 262570), alpha-glucosidase inhibitors (e.g. acarbose, voglibose),

35 alpha2 antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues

5 (e.g. exendin-4) or amylin. Also, inhibitors of protein tyrosine phosphatase 1, substances which influence deregulated glucose production in the liver, such as e.g. inhibitors of glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol pyruvate carboxykinase, glycogen synthase kinase or pyruvate  
10 dehydrokinase, lipid lowering agents, such as HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate, fenofibrate), nicotinic acid and its derivatives, cholesterol absorption inhibitors such as for example ezetimibe, bile acid-binding substances such as for example cholestyramine, HDL-raising compounds such as for example inhibitors of CETP or regulators of ABC1 or  
15 active substances for the treatment of obesity, such as e.g. sibutramine or tetrahydrolipostatin, or  $\beta_3$ -agonists such as SB-418790 or AD-9677. It is also possible to combine the compounds with drugs for treating high blood pressure such as e.g. All antagonists or ACE inhibitors, diuretics,  $\beta$ -blockers, etc., or combinations thereof.

20

The dosage required to achieve such an effect is expediently, by intravenous route, 1 to 100 mg, preferably 1 to 30 mg, and by oral route 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention, optionally combined  
25 with other active substances, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol,  
30 carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

35 The Examples that follow are intended to illustrate the invention:

5

Preparation of the starting compounds:

Example I

10

1-[(benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxy-carbonylamino)-piperidin-1-yl]-xanthine

91 µl of benzyl chloracetate are added to 242 mg of 3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine and 110 mg  
 15 potassium carbonate in 2 ml N,N-dimethylformamide and the reaction mixture is shaken for about three hours at 55°C. Then the cooled reaction mixture is combined with 5 ml methylene chloride and 15 ml of water and the organic phase is separated off. The aqueous phase is extracted with methylene chloride and the combined organic phases are dried and evaporated down.

20 Yield: 213 mg (65 % of theory)

$R_f$  value: 0.82 (silica gel, cyclohexane/ethyl acetate = 2:8)

Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 565 [M+H]<sup>+</sup>

The following compounds are obtained analogously to Example I:

25

(1) 1-[(benzylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 564 [M+H]<sup>+</sup>

30 (2) 1-[(phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

$R_f$  value: 0.60 (silica gel, cyclohexane/ethyl acetate = 2:8)

Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 550 [M+H]<sup>+</sup>

- 5 (3) 1-[[[(pyridin-2-yl)aminocarbonyl]methyl]-3-methyl-7-(2-butyln-1-yl)-8-[(R)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
Mass spectrum (ESI<sup>+</sup>): m/z = 551 [M+H]<sup>+</sup>
- (4) 1-[[[(pyridin-3-yl)methoxycarbonyl]methyl]-3-methyl-7-(2-butyln-1-yl)-8-[(R)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
10 Mass spectrum (ESI<sup>+</sup>): m/z = 566 [M+H]<sup>+</sup>
- (5) 1-[[[(pyridin-3-yl)aminocarbonyl]methyl]-3-methyl-7-(2-butyln-1-yl)-8-[(R)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
15 Mass spectrum (ESI<sup>+</sup>): m/z = 551 [M+H]<sup>+</sup>
- (6) 1-[[[(2-methyl-phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-[(R)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
Mass spectrum (ESI<sup>+</sup>): m/z = 564 [M+H]<sup>+</sup>  
20
- (7) 1-[[[(2-nitro-phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-[(R)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
Mass spectrum (ESI<sup>+</sup>): m/z = 595 [M+H]<sup>+</sup>
- 25 (8) 1-[[[(4-cyano-phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-bromo-xanthine  
Mass spectrum (ESI<sup>+</sup>): m/z = 455, 457 [M+H]<sup>+</sup>
- (9) 1-[[[(2-methoxy-phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-[(R)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
30 Mass spectrum (ESI<sup>+</sup>): m/z = 580 [M+H]<sup>+</sup>
- (10) 1-methoxycarbonylmethyl-3-methyl-7-(2-butyln-1-yl)-8-[3-(tert.-butyloxy-carbonylamino)-piperidin-1-yl]-xanthine  
35 R<sub>f</sub> value: 0.40 (silica gel, cyclohexane/ethyl acetate = 5:6)

5 Mass spectrum (ESI<sup>+</sup>): m/z = 489 [M+H]<sup>+</sup>

(11) 1-methoxycarbonylmethyl-3-methyl-7-(2-butyln-1-yl)-8-[(*R*)-3-(tert.-butyloxy-carbonylamino)-piperidin-1-yl]-xanthine

R<sub>f</sub> value: 0.82 (silica gel, methylene chloride/methanol/conc. aqueous ammonia =  
10 90:10:1)

Mass spectrum (ESI<sup>+</sup>): m/z = 489 [M+H]<sup>+</sup>

(12) 1-[(3-cyano-phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-bromo-xanthine

15 Mass spectrum (ESI<sup>+</sup>): m/z = 455,457 [M+H]<sup>+</sup>

(13) 1-[(3-methoxy-benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

Mass spectrum (ESI<sup>+</sup>): m/z = 595 [M+H]<sup>+</sup>

20

(14) 1-[(3-nitro-benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

Mass spectrum (ESI<sup>+</sup>): m/z = 610 [M+H]<sup>+</sup>

25

#### Example II

3-methyl-7-(2-butyln-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

30 11.00 g of (*R*)-3-tert.-butyloxycarbonylamino-piperidine are added to 15.00 g of 3-methyl-7-(2-butyln-1-yl)-8-bromo-xanthine and 16.00 g of potassium carbonate in 100 ml dimethylsulphoxide and the thick, light beige suspension is stirred for four hours at approx. 114°C with a mechanical stirrer. Then another 900 mg of (*R*)-3-tert.-butyloxycarbonylamino-piperidine, dissolved in 10 ml of dimethylsulphoxide,  
35 are added to the reaction mixture which is then stirred for a further two hours at



5 114°C. After cooling to ambient temperature the reaction mixture is diluted with  
copious amounts of water. The precipitate formed is thoroughly triturated until  
there are no lumps remaining, and suction filtered. The light-coloured solid is again  
suspended with water, suction filtered, washed with water and diethyl ether and  
dried at 60°C in the circulating air dryer.

10 Yield: 19.73 g (94 % of theory)  
R<sub>f</sub> value: 0.64 (silica gel, ethyl acetate)  
Mass spectrum (ESI<sup>+</sup>): m/z = 417 [M+H]<sup>+</sup>

The following compounds are obtained analogously to Example II:

15 (1) 1-[(4-cyano-phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-  
butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
Mass spectrum (ESI<sup>+</sup>): m/z = 575 [M+H]<sup>+</sup>

20 (2) 1-(2-hydroxy-3-phenoxy-propyl)-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxy-  
carbonylamino)-piperidin-1-yl]-xanthine  
Mass spectrum (ESI<sup>+</sup>): m/z = 567 [M+H]<sup>+</sup>

(3) 3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-  
25 xanthine  
melting point: 235-237°C  
Mass spectrum (ESI<sup>+</sup>): m/z = 417 [M+H]<sup>+</sup>

(4) 1-[(3-cyano-phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-  
30 butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
Mass spectrum (ESI<sup>+</sup>): m/z = 575 [M+H]<sup>+</sup>

35

5 Example III3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine

17.06 g 1-bromo-2-butyn are added to 30.17 g of 3-methyl-8-bromo-xanthine and 27.00 ml of Hünig base in 370 ml of N,N-dimethylformamide. The reaction mixture  
 10 is stirred for two hours at ambient temperature, then another 1 ml of 1-bromo-2-butyn and stirring is continued for a further hour at ambient temperature. For working up the reaction mixture is diluted with approx. 300 ml of water and the light-coloured precipitate formed is suction filtered and washed with water. The filter cake is washed with a little ethanol and diethyl ether and dried at 60°C in the  
 15 circulating air dryer.

Yield: 30.50 g (84 % of theory)

R<sub>f</sub> value: 0.24 (silica gel, methylene chloride/methanol = 95:5)

Mass spectrum (ESI<sup>+</sup>): m/z = 297, 299 [M+H]<sup>+</sup>

20

Example IV
1-(2-oxo-3-phenoxy-propyl)-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

25 A solution of 107 µl dimethylsulphoxide in 0.5 ml methylene chloride is added dropwise to 64 µl oxalyl chloride in 2 ml methylene chloride with stirring at -60°C. After five minutes a solution of 345 mg of 1-(2-hydroxy-3-phenoxy-propyl)-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
 30 in 1.5 ml methylene chloride is added dropwise and after another 15 minutes 0.42 ml of triethylamine are added. Then the cooling bath is removed and the reaction mixture is allowed to warm up to ambient temperature. For working up it is diluted with methylene chloride and washed with water. The organic phase is dried over magnesium sulphate, evaporated down and chromatographed through a silica gel  
 35 column with cyclohexane/ethyl acetate (4:1 to 1:1) as eluant.

- 5 Yield: 241 mg (70 % of theory)  
Mass spectrum (ESI<sup>+</sup>): m/z = 565 [M+H]<sup>+</sup>

Example V

- 10 1-(2-hydroxy-3-phenoxy-propyl)-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine  
556 mg of 2-phoxymethyl-oxirane and 110 mg of potassium iodide are added to  
a mixture of 1.00 g 3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine and 677 mg of  
potassium carbonate in 25 ml of N,N-dimethylformamide. The reaction mixture is  
15 stirred for approx. eight hours at 120°C. For working up it is diluted with water and  
extracted with ethyl acetate. The combined extracts are dried over magnesium  
sulphate, evaporated down and chromatographed through a silica gel column with  
cyclohexane/ethyl acetate (4:1 to 1:1) as eluant.  
Yield: 446 mg (30 % of theory)  
Mass spectrum (ESI<sup>+</sup>): m/z = 447, 449 [M+H]<sup>+</sup>

20

Example VI

- 1-[(2-amino-benzylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-  
25 butyloxycarbonylamino)-piperidin-1-yl]-xanthine  
162 mg of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate are  
added to a mixture of 250 mg of 1-carboxymethyl-3-methyl-7-(2-butyn-1-yl)-8-[3-  
(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine, 64 mg of 2-amino-  
benzylamine and 265 µl of Hünig base in 3 ml of N,N-dimethylformamide. The  
30 reaction mixture is stirred for about two hours at ambient temperature and then  
evaporated down. The residue is triturated with 15 ml of 1 N sodium hydroxide  
solution and suction filtered. The filter cake is washed with a little ethanol and  
diethyl ether and dried.  
Yield: 228 mg (78 % of theory)  
35 R<sub>f</sub> value: 0.55 (silica gel, methylene chloride/methanol = 9:1)

- 5 Mass spectrum (ESI<sup>+</sup>): m/z = 579 [M+H]<sup>+</sup>

The following compounds are obtained analogously to Example VI:

- (1) 1-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-  
10 [(*R*)-3-(tert.-butoxycarbonylamino)-piperidin-1-yl]-xanthine

R<sub>f</sub> value: 0.65 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI<sup>+</sup>): m/z = 590 [M+H]<sup>+</sup>

- 15 (2) 1-[2-(3,4-dihydro-2*H*-quinolin-1-yl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-  
[(*R*)-3-(tert.-butoxycarbonylamino)-piperidin-1-yl]-xanthine

R<sub>f</sub> value: 0.70 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI<sup>+</sup>): m/z = 590 [M+H]<sup>+</sup>

20

#### Example VII

1-carboxymethyl-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butoxycarbonylamino)-  
piperidin-1-yl]-xanthine

- 25 Prepared by saponifying 1-methoxycarbonylmethyl-3-methyl-7-(2-butyn-1-yl)-8-[3-  
(tert.-butoxycarbonylamino)-piperidin-1-yl]-xanthine with 4 N potassium  
hydroxide solution in a mixture of tetrahydrofuran and methanol (5:1) at ambient  
temperature.

Mass spectrum (ESI<sup>+</sup>): m/z = 475 [M+H]<sup>+</sup>

30

The following compounds are obtained analogously to Example VII:

(1) 1-carboxymethyl-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-  
butoxycarbonylamino)-piperidin-1-yl]-xanthine

- 5  $R_f$  value: 0.23 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 80:20:1)

Mass spectrum (ESI<sup>-</sup>):  $m/z$  = 473 [M-H]<sup>-</sup>

10 Example VIII

(3-Methoxy-benzyl) chloroacetate

- 1 ml of chloroacetyl chloride is added dropwise to 1.49 ml of 3-methoxybenzyl alcohol and 1.05 ml of pyridine in 50 ml dichloromethane while cooling with an ice bath. After the addition has ended the reaction mixture is stirred for a further 30 minutes at ambient temperature. For working up it is combined with water and the aqueous phase is extracted several times with methylene chloride. The combined organic phases are dried over magnesium sulphate and evaporated down.

Yield: 2.35 g (87 % of theory)

- 20 Mass spectrum (EI):  $m/z$  = 214, 216 [M]<sup>+</sup>

The following compounds are obtained analogously to Example VIII:

(1) (3-nitro-benzyl)-chloroacetate

- 25 Mass spectrum (EI):  $m/z$  = 229, 231 [M]<sup>+</sup>

Preparation of the final compounds:

30 Example 1

1-[(benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(R)-3-amino-piperidin-1-yl]-xanthine

- 213 mg of 1-[(benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(R)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine in 2 ml methylene chloride are combined with 1 ml of trifluoroacetic acid and the reaction mixture is shaken for 20

5 minutes at 30°C. For working up it is made alkaline with 15 ml of 1 N sodium hydroxide solution and the organic phase is separated off. The aqueous phase is extracted with methylene chloride and the combined organic phases are evaporated down. The flask residue is purified through a silica gel column with methylene chloride/methanol (100:0 to 70:30) as eluant.

10 Yield: 170 mg (97 % of theory)

Mass spectrum (ESI<sup>+</sup>): m/z = 465 [M+H]<sup>+</sup>

15

The following compounds are obtained analogously to Example 1:

(1) 1-[(benzylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

20 Mass spectrum (ESI<sup>+</sup>): m/z = 464 [M+H]<sup>+</sup>

(2) 1-[(phenylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

Mass spectrum (ESI<sup>+</sup>): m/z = 450 [M+H]<sup>+</sup>

25

(3) 1-[(pyridin-2-yl)aminocarbonyl]methyl-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

R<sub>f</sub> value: 0.55 (Ready-made reversed phase TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:0.1)

30 Mass spectrum (ESI<sup>+</sup>): m/z = 451 [M+H]<sup>+</sup>

(4) 1-[(pyridin-3-yl)methoxycarbonyl]methyl-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

R<sub>f</sub> value: 0.40 (silica gel, methylene chloride/methanol/triethylamine = 90:10:1)

35 Mass spectrum (ESI<sup>+</sup>): m/z = 466 [M+H]<sup>+</sup>

5

(5) 1-[[[(pyridin-3-yl)aminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

Mass spectrum (ESI<sup>+</sup>):  $m/z = 451$  [M+H]<sup>+</sup>

10

(6) 1-[[[(2-methyl-phenyl)aminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

Mass spectrum (ESI<sup>+</sup>):  $m/z = 464$  [M+H]<sup>+</sup>

15

(7) 1-[[[(2-nitro-phenyl)aminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

Mass spectrum (ESI<sup>+</sup>):  $m/z = 495$  [M+H]<sup>+</sup>

20

(8) 1-[[[(4-cyano-phenyl)aminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI<sup>+</sup>):  $m/z = 475$  [M+H]<sup>+</sup>

25

(9) 1-[[[(2-methoxy-phenyl)aminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

Mass spectrum (ESI<sup>+</sup>):  $m/z = 480$  [M+H]<sup>+</sup>

30

(10) 1-(2-oxo-3-phenoxy-propyl)-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI<sup>+</sup>):  $m/z = 465$  [M+H]<sup>+</sup>

35

(11) 1-[[[(2-amino-benzylaminocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI<sup>+</sup>):  $m/z = 479$  [M+H]<sup>+</sup>

(12) 1-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*R*)-3-amino-piperidin-1-yl]-xanthine

- 5      $R_f$  value: 0.15 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 490 [M+H]<sup>+</sup>

- (13) 1-[2-(3,4-dihydro-2*H*-quinolin-1-yl)-2-oxo-ethyl]-3-methyl-7-(2-butyne-1-yl)-8-  
10     [(*R*)-3-amino-piperidin-1-yl]-xanthine

$R_f$  value: 0.09 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 490 [M+H]<sup>+</sup>

- 15     (14) 1-[[3-(3-cyano-phenyl)aminocarbonyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine x trifluoroacetic acid

Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 475 [M+H]<sup>+</sup>

- (15) 1-[[3-(3-methoxy-benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(*R*)-3-  
20     amino-piperidin-1-yl]-xanthine

Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 495 [M+H]<sup>+</sup>

- (16) 1-[[3-(3-nitro-benzyloxycarbonyl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-[(*R*)-3-  
amino-piperidin-1-yl]-xanthine

- 25     Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 510 [M+H]<sup>+</sup>

The following compounds may also be prepared analogously to the foregoing  
Examples and other methods known from the literature:

- 30     (1) 1-[[3-(pyrimidin-2-yl)aminocarbonyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

- (2) 1-[[3-(pyrimidin-4-yl)aminocarbonyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

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- 5 (3) 1-[[pyridin-4-yl]aminocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-  
piperidin-1-yl)-xanthine
- (4) 1-[[N-(pyridin-2-yl)-N-methylaminocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-  
10 (3-amino-piperidin-1-yl)-xanthine
- (5) 1-[[4-nitrophenyl]aminocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-  
piperidin-1-yl)-xanthine
- (6) 1-[[4-cyano-2-fluorophenyl]aminocarbonyl]methyl}-3-methyl-7-(1-buten-1-yl)-8-  
15 (3-amino-piperidin-1-yl)-xanthine
- (7) 1-[[4-methylphenyl]aminocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-  
amino-piperidin-1-yl)-xanthine
- 20 (8) 1-[[2-cyanophenyl]aminocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-  
amino-piperidin-1-yl)-xanthine
- (9) 1-[[3-cyano-5-chlorophenyl]aminocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-  
8-(3-amino-piperidin-1-yl)-xanthine  
25
- (10) 1-[[pentafluorophenyl]aminocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-  
amino-piperidin-1-yl)-xanthine
- (11) 1-[[6-cyano-2-pyridinyl]aminocarbonyl]methyl}-3-methyl-7-(3-methyl-2-buten-  
30 1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (12) 1-[[6-methylpyridin-2-yl]aminocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-  
(3-amino-piperidin-1-yl)-xanthine

- 5 (13) 1-[[[(5-methylpyridin-2-yl)aminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-  
[N-(2-aminoethyl)-N-methylamino]-xanthine
- (14) 1-[[[(4-methylpyridin-2-yl)aminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-  
(3-amino-piperidin-1-yl)-xanthine
- 10 (15) 1-[[[(3-methylpyridin-2-yl)aminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-  
(3-amino-piperidin-1-yl)-xanthine
- (16) 1-[[[1-(pyridin-3-yl)ethylaminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-  
15 amino-piperidin-1-yl)-xanthine
- (17) 1-[[[N-(pyridin-3-ylmethyl)-N-methylaminocarbonyl]methyl]-3-methyl-7-(2-  
butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 20 (18) 1-[[[(pyridin-2-yl)methylaminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-  
amino-piperidin-1-yl)-xanthine
- (19) 1-[[[(pyridin-4-yl)methylaminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-  
amino-piperidin-1-yl)-xanthine
- 25 (20) 1-[[[(3-cyanophenyl)methylaminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-  
(3-amino-piperidin-1-yl)-xanthine
- (21) 1-[[[(3-nitrophenyl)methylaminocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-  
30 (3-amino-piperidin-1-yl)-xanthine
- (22) 1-[[[N'-(pyridin-2-yl)hydrazinocarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-  
amino-piperidin-1-yl)-xanthine

- 5 (23) 1-{{[N'-(pyridin-3-yl)hydrazinocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (24) 1-{{[N'-(pyridin-4-yl)hydrazinocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 10 (25) 1-(phenyloxycarbonylmethyl)-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (26) 1-{{[(pyridin-4-yl)methoxycarbonyl]methyl}-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 15 (27) 1-{{[(pyridin-2-yl)methoxycarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (28) 1-{{[(pyrimidin-5-yl)methoxycarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 20 (29) 1-{{[1-(2-methoxyphenyl)ethoxycarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 25 (30) 1-{{[(2,6-dichloro-4-trifluoromethylphenyl)methoxycarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-[N-(2-aminoethyl)-N-methylamino]-xanthine
- (31) 1-{{[(pentafluorophenyl)methoxycarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 30 (32) 1-{{[(3-trifluoromethoxyphenyl)methoxycarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

- 5 (33) 1-[[[(3,5-dicyanophenyl)methoxycarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (34) 1-[(phenylaminomethylcarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 10 (35) 1-[[[(pyridin-3-yl)aminomethylcarbonyl]methyl]-3-methyl-7-(1-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (36) 1-[[[(pyridin-2-yl)aminomethylcarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 15 (37) 1-[[[(pyridin-4-yl)aminomethylcarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (38) 1-[[[N-(pyridin-3-yl)-N-methylaminomethylcarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 20 (39) 1-[[[(pentafluorophenoxy)methylcarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 25 (40) 1-[[[(2-nitrophenoxy)methylcarbonyl]methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (41) 1-[[[(3-methylsulphonylphenoxy)methylcarbonyl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 30 (42) 1-[[[(1H-pyrrol-2-yloxy)methylcarbonyl]methyl]-3-methyl-7-(2-buten-1-yl)-8-(3-amino-pyrrolidin-1-yl)-xanthine

- 5 (43) 1-{{{(pyridin-3-yloxy)methylcarbonyl}methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (44) 1-{{{(pyridin-2-yloxy)methylcarbonyl}methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 10 (45) 1-{{{(pyridin-4-yloxy)methylcarbonyl}methyl}-3-methyl-7-[(1-cyclopentenyl)-methyl]-8-[N-(2-aminoethyl)-N-methylamino]-xanthine
- (46) 1-{{{(phenylsulphanyl)methylcarbonyl}methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 15 (47) 1-{{{(phenylsulphinyl)methylcarbonyl}methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (48) 1-{{{(phenylsulphonyl)methylcarbonyl}methyl}-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 20 (49) 1-[(phenylaminothiocarbonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 25 (50) 1-{{{(pyridin-2-yl)aminothiocarbonyl}methyl}-3-methyl-7-(2-butyn-1-yl)-8-[N-(2-aminoethyl)-N-methylamino]-xanthine
- (51) 1-{{{(pyridin-4-yl)aminothiocarbonyl}methyl}-3-methyl-7-(2-butyn-1-yl)-8-[N-(2-aminoethyl)-N-methylamino]-xanthine
- 30 (52) 1-{{{[N-(pyridin-3-yl)-N-methylaminothiocarbonyl]methyl}-3-methyl-7-(2-butyn-1-yl)-8-[N-(2-aminoethyl)-N-methylamino]-xanthine

- 5 (53) 1-[[[(3-methylphenyl)aminothiobonyl]methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (54) 1-[[[(2-methoxyphenyl)aminothiobonyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 10 (55) 1-[[[(4-cyanophenyl)aminothiobonyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (56) 1-[(N-phenylcarbamimidoyl)methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-  
15 piperidin-1-yl)-xanthine
- (57) 1-[[[N-(phenylamino)-N'-cyano-carbamimidoyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 20 (58) 1-[3-cyano-2-(phenylamino)-2-propen-1-yl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (59) 1-[3-cyano-2-(pyridin-2-ylamino)-2-propen-1-yl]-3-methyl-7-(2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 25 (60) 1-[3-cyano-2-[N-(pyridin-2-yl)-N-methylamino]-2-propen-1-yl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (61) 1-[3-cyano-2-(pyridin-4-ylamino)-2-propen-1-yl]-3-methyl-7-(2-butyne-1-yl)-8-  
30 (3-amino-piperidin-1-yl)-xanthine
- (62) 1-[2-(pyridin-4-ylamino)-3-trifluoromethyl-2-propen-1-yl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

- 5 (63) 1-[3-nitro-2-(pyridin-2-ylamino)-2-propen-1-yl]-3-methyl-7-[(1-cyclopentenyl)-methyl]-8-(3-amino-piperidin-1-yl)-xanthine
- (64) 1-[2-(3-cyanophenylamino)-3-methylsulphinyl-2-propen-1-yl]-3-methyl-7-[(1-cyclopentenyl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine
- 10 (65) 1-[2-(pyridin-4-ylamino)-3-methylsulphonyl-2-propen-1-yl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (66) 1-[2-(phenylamino)-3-(pyrimidin-2-yl)-2-propen-1-yl]-3-methyl-7-(3-methyl-2-
- 15 buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (67) 1-[3,3-dicyano-2-(phenylamino)-2-propen-1-yl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 20 (68) 1-[3-cyano-3-fluoro-2-(phenylamino)-2-propen-1-yl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (69) 1-[(phenylaminosulphonyl)methyl]-3-methyl-7-(2-buten-1-yl)-8-[N-(2-aminoethyl)-N-methylamino]-xanthine
- 25 (70) 1-[[{(pyridin-2-yl)aminosulphonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (71) 1-[[{(pyridin-3-ylmethyl)aminosulphonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-
- 30 amino-piperidin-1-yl)-xanthine
- (72) 1-[[N-(pyridin-3-ylmethyl)-N-methylaminosulphonyl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

- 5 (73) 1-[(phenyloxymethylsulphinyl)methyl]-3-methyl-7-(1-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (74) 1-[[pyridin-3-yloxy)methylsulphanyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-pyrrolidin-1-yl)-xanthine
- 10 (75) 1-[(phenylamino)methylsulphanyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (76) 1-[[pyridin-3-ylamino)methylsulphanyl]methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 15 (77) 1-[(phenyloxymethylsulphonyl)methyl]-3-methyl-7-(2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (78) 1-[[pyridin-3-yloxy)methylsulphonyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 20 (79) 1-[(phenylaminomethylsulphonyl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- 25 (80) 1-[[pyridin-3-ylamino)methylsulphonyl]methyl]-3-methyl-7-(2-butyne-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

## Example 2

30

### Coated tablets containing 75 mg of active substance

1 tablet core contains:

	active substance	75.0 mg
35	calcium phosphate	93.0 mg



5	corn starch	35.5 mg
	polyvinylpyrrolidone	10.0 mg
	hydroxypropylmethylcellulose	15.0 mg
	magnesium stearate	<u>1.5 mg</u>
		230.0 mg

10

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

15

Weight of core: 230 mg

20

die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

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Example 3Tablets containing 100 mg of active substanceComposition:

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1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
35 magnesium stearate	<u>2.0 mg</u>

5 220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier  
 10 at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar, faceted on both sides and notched on one side.

15 Example 4

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

20	active substance	150.0 mg
	powdered lactose	89.0 mg
	corn starch	40.0 mg
	colloidal silica	10.0 mg
	polyvinylpyrrolidone	10.0 mg
25	magnesium stearate	<u>1.0 mg</u>
		300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a  
 30 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

35 die: 10 mm, flat

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Example 5Hard gelatine capsules containing 150 mg of active substance

10	1 capsule contains:		
	active substance		150.0 mg
	corn starch (dried)	approx.	80.0 mg
	lactose (powdered)	approx.	87.0 mg
	magnesium stearate		<u>3.0 mg</u>
15		approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The

20 finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

Example 625 Suppositories containing 150 mg of active substance

	1 suppository contains:		
	active substance		150.0 mg
	polyethyleneglycol 1500		550.0 mg
30	polyethyleneglycol 6000		460.0 mg
	polyoxyethylene sorbitan monostearate		<u>840.0 mg</u>
			2,000.0 mg

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5 Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 710 Suspension containing 50 mg of active substance

100 ml of suspension contain:

	active substance	1.00 g
	carboxymethylcellulose-Na-salt	0.10 g
15	methyl p-hydroxybenzoate	0.05 g
	propyl p-hydroxybenzoate	0.01 g
	glucose	10.00 g
	glycerol	5.00 g
	70% sorbitol solution	20.00 g
20	flavouring	0.30 g
	dist. water	ad 100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

30 5 ml of suspension contain 50 mg of active substance.

Example 8Ampoules containing 10 mg active substance

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5    **Composition:**

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

10    **Preparation:**

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

**Example 9**

15    **Ampoules containing 50 mg of active substance**

**Composition:**

active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
20    double-distilled water	ad	10.0 ml

**Preparation:**

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

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The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such

30    modifications are intended to fall within the scope of the appended claims.